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Case Series

Paediatrics Section

Transient Neonatal Hyperparathyroidism Unfolding a Noteworthy Cause: A Series of Four Cases

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ABSTRACT

Transient Neonatal Hyperparathyroidism (TNHP) is an abnormal bone disorder caused by impaired maternal-foetal calcium transport across the placenta, leading to inadequate foetal bone mineralisation. It is caused by mutations in the gene encoding the Transient Receptor Potential Channel, Subfamily V, Member 6 (TRPV6), which is involved in maternal-to-foetal calcium transport. The TRPV6 mutation results in hypocalcaemia in the foetus, leading to skeletal deformities such as narrow chest walls, multiple rib fractures, bowing of long bones, and generalised osteopenia. Babies are usually born with respiratory distress that requires ventilatory support due to a pliable chest wall. The skeletal abnormalities closely resemble those of osteogenesis imperfecta, skeletal dysplasias and congenital rickets. All four cases described in this series presented with clinical features of undermineralisation of bone and chest wall deformities resembling congenital rickets or osteogenesis imperfecta. One case of suspected osteogenesis imperfecta was found to have a homozygous variant in the TRPV6 gene upon genetic testing. The other three cases presented with respiratory distress after birth and had homozygous variants in the same gene (TRPV6). In newborns, similar clinical presentations coupled with the presence of hyperparathyroidism should raise suspicion of TNHP. Genetic studies may reveal homozygous or compound heterozygous variants in the TRPV6 gene. There will be significant clinical improvement with treatment using oral calcium, as the intestinal transport of calcium becomes effective after birth. Early identification of this transient condition is helpful for timely management.

Keywords: Calcium homeostasis, Newborn, Osteopenia, Skeletal dysplasia

INTRODUCTION

Calcium is an important mineral essential for many physiological functions of the human body, such as the mineralisation of bones, neuromuscular transmission and blood coagulation. The transport of calcium from the mother to the foetus through the placenta plays a major role in foetal calcium homeostasis [1]. Calcium transport occurs through different mechanisms, of which TRPV6, a highly calcium-selective channel in the placenta, is suggested to have a critical role. Mutations in the gene encoding TRPV6 have been recognised to cause TNHP due to inadequate maternal-to-foetal calcium transport through the placenta [2]. This results in foetal hypocalcaemia and secondary hyperparathyroidism, leading to increased bone resorption.

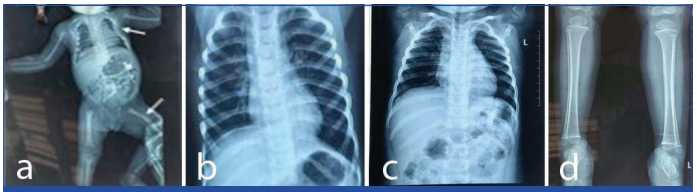
Alterations in TRPV6 in the foetus cause short bones with impaired mineralisation. Babies are born with severe skeletal deformities, such as a narrow bell-shaped chest, osteopenia and multiple fractures [3,4]. This condition clinically resembles osteogenesis imperfecta, skeletal dysplasias and congenital rickets [5]. In this series of four cases, the first was diagnosed only after genetic testing. The other cases were suspected to have the condition due to their resemblance to the previous case and were later confirmed by genetic testing. This highlights the importance of identifying this condition in neonates with features of skeletal dysplasias and fractures, allowing for timely intervention.

CASE SERIES

Case 1

A two-month-old term female baby of non consanguineous parents was referred to the genetics clinic as a suspected case of osteogenesis imperfecta at birth. The baby was brought in late, at two months of age, due to travel restrictions during the COVID-19 pandemic. Upon examination, the baby was active and feeding well.

The medical records indicated that the baby had an APGAR score of 9 at one minute, a heart rate of 140 beats per minute and a respiratory rate of 52 breaths per minute. The baby was born by elective caesarean section (indication: breech), and the immediate postnatal period was uneventful. An antenatal ultrasound performed at 34 weeks showed rhizomelic shortening of both upper and lower limbs. There was no history of maternal co-morbidities or habits, and there was no significant family history. The baby had a birth weight of 2518 g, a length of 46 cm, and a head circumference of 33 cm, with minor dysmorphic features such as a prominent forehead, low-set ears, and a high-arched palate. There was no respiratory distress or feeding difficulties. However, the infantogram showed a bell-shaped thoracic cage, multiple rib fractures, and diffuse osteopenia of the vertebral bodies and long bones [Table/Fig-1a]. Postnatal evaluation revealed normal serum calcium (8.2 mg/dL), normal phosphorus (4.5 mg/dL), normal alkaline phosphatase (338 U/L), and low vitamin D levels (8.93 ng/mL) [Table/Fig-2]. Parathormone levels at birth and the mother's vitamin D values were not available. The baby was given oral calcium at 500 mg/day and vitamin D at 400 IU/day. With a clinical diagnosis of osteogenesis imperfecta, the mother was advised to handle the baby with utmost care to avoid fractures.



[Table/Fig-1]: a) Infantogram at birth- bell shaped thorax, osteopenia, bowing left femur; b) Follow-up X-ray at 1 year of age- chest X-ray: normal rib cage; Follow-up X-ray at 2 years age- chest X-ray: normal rib cage; d) X-ray lower limbs-normal, no bowing.

Upon evaluation in the genetics clinic at two months of age, the growth parameters were normal (weight: 3.82 kg, length: 52 cm, and head circumference: 36 cm), and development was appropriate for age. There were no blue sclera, skeletal deformities, or dysmorphic features, except for a prominent forehead. Investigations showed

Case	Prenatal period	Clinical features at birth	Radiological features	Laboratory values						Age at complete resolution
				Age	Calcium (mg/dL)	Phosphorus (mg/dL)	ALP (U/L)	PTH (pg/mL)	Vitamin D (ng/mL)	
Case 1	Rhizomelic dwarfism	Normal newborn period	Bell shaped thorax multiple rib fractures Osteopenia	Birth	8.2	4.5	338	Not done	8.93	1 year
				4 weeks	*	*	*	*	*	
Case 2	Polyhydramnios	Respiratory distress Severe hypotonia Narrow chest wall Bowing of long bones Length- 3rd centile	Bell shaped thorax Osteopenia Thin and short ribs with costochondral beading	Birth	8	5.2	253	1476	8	1 year 9 months Bilateral mild bowing of femur
				4 weeks	10.8	4.7	614	102	76	
Case 3	Polyhydramnios	Respiratory distress Severe hypotonia Narrow chest wall Bowing of long bones Length- 10th centile	Bell shaped thorax Osteopenia Thin ribs multiple rib fractures with callus	Birth	8.5	4.8	179	1966	6.5	1 year 6 months
				4 weeks	9.4	5.8	330	152	68.9	
Case 4	Oligohydramnios	Respiratory distress Severe hypotonia Narrow chest wall Length- 3rd centile	Bell shaped thorax Osteopenia Multiple rib fractures	Birth	8.2	4.5	338	1347	11.05	1 year 6 months
				4 weeks	10.4	5.9	308	158	78	

[Table/Fig-2]: Clinical and laboratory profile.
ALP: Alkaline phosphatase; PTH: Parathormone; Normal range in newborn: Calcium- 9-11.2 mg/dL, Phosphorus- 4.5-8 mg/dL, ALP- 150-600 U/L, PTH- 15-72 pg/mL, Vitamin D- 20-50 ng/mL
*Follow-up biochemical investigations of case 1 were not done as the diagnosis was considered as osteogenesis imperfecta, and referred to our clinic for genetic study

normal serum calcium (10.7 mg/dL), normal phosphorus (6.39 mg/dL), normal ALP (661 U/L), and normal vitamin D levels (44 ng/mL). A genetic study was conducted for suspected osteogenesis imperfecta, which revealed a homozygous 3' splice site variation (c.347-1G>A) in intron 2 of the TRPV6 gene that affects the invariant AG acceptor splice site of exon 2, classified as a pathogenic variant according to American College of Medical Genetics (ACMG) guidelines [6]. This diagnosis was consistent with TNHP inherited in an autosomal recessive pattern. As the biochemical parameters were normal, the baby was continued on routine vitamin D at 400 IU/day until one year of age. Upon follow-up at two years of age, physical examination findings and radiological features were normal [Table/Fig-1b-d].

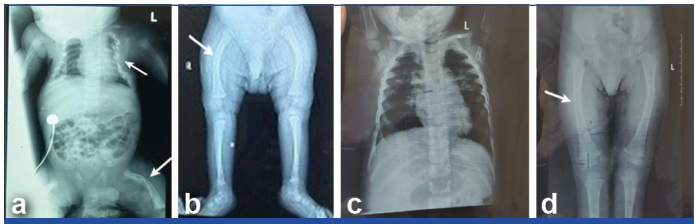
Case 2

A term, 37-week-old male baby, the second born of a non consanguineous marriage, was small for gestational age (birth weight: 1850 g). He was delivered via caesarean section (indication: previous CS) and was referred to the neonatal intensive care unit with worsening respiratory distress soon after birth and bowing of the legs, with a suspicion of osteogenesis imperfecta.

On examination, the baby had a respiratory rate of 70 breaths per minute, a heart rate of 150 beats per minute, and an SpO_2 of 82%. He was given non invasive ventilation. Antenatal details showed polyhydramnios (AFI 18 cm) but no other maternal co-morbidities. The baby measured 42 cm in length, had a head circumference of 31 cm, a narrow chest wall, and bilateral bowing of the lower limbs.

The biochemical parameters showed normal serum calcium (8 mg/dL) and normal serum phosphorus (5.2 mg/dL), but elevated parathormone levels (PTH - 1476 pg/mL) and low vitamin D levels (8 ng/mL) [Table/Fig-2]. Maternal vitamin D levels were insufficient (16 ng/mL). X-rays revealed bowing of both femurs, narrow beaded ribs, and osteopenia of long bones and vertebral bodies [Table/Fig-3a]. Considering the possibility of congenital rickets due to insufficient maternal vitamin D levels, the baby was treated with vitamin D 2000 IU/day for one week, followed by 400 IU/day, along with oral calcium 500 mg/day. The baby was weaned off ventilation on postnatal day 3 to nasal Continuous Positive Airway Pressure (CPAP) and transitioned to room air on postnatal day 10.

Repeat investigations conducted after two weeks showed normal serum calcium (8.8 mg/dL), normal serum phosphorus (5.4 mg/dL), and lowered PTH levels (453 pg/mL). Given the clinical presentation of a narrow chest wall, osteopenia, multiple rib fractures, and elevated parathormone levels with normal calcium and phosphorus, TNHP was suspected, and a genetic study was performed. This identified a homozygous 3' splice site variation (c.347-1G>A) in intron 2 of the TRPV6 gene, confirming the diagnosis of TNHP [Table/Fig-4]. At discharge, the baby was prescribed vitamin D 400 IU/day, which was advised to continue until one year of age. Follow-up was conducted at regular intervals of three months, and by one year and nine months of age, the baby exhibited mild bowing of the femurs [Table/Fig-3b-d].



[Table/Fig-3]: (a-d) a) Infantogram at birth-bellshaped thorax, multiple rib fractures with callus, generalised osteopenia, bowing left femur; b) X-ray lower limbs at 8 months- mild osteopenia, bilateral bowing femur. At 1 year 9 months; c) Chest X-ray- normal rib cage, bone mineralisation normal; d) X-ray lower limbs at 1 year 9 months- mild bowing of femur.

Case 3

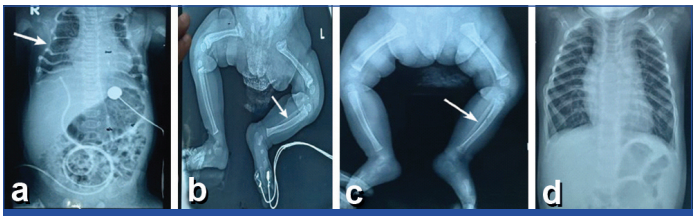
A term (40-week, two-day-old) female baby, born from a non consanguineous marriage and appropriate for gestational age (birth weight: 3160 g), was delivered via caesarean section due to the indication of thick Meconium-Stained Amniotic Fluid (MSAF). She was referred for respiratory distress soon after birth. There were no maternal co-morbidities, and no significant family history. Upon arrival, the baby exhibited a respiratory rate of 96 breaths per minute, with subcostal and intercostal retractions, a heart rate of 140 beats per minute, and was admitted to the newborn intensive care unit

Case	Gene	Location	Variant	Zygosity	Disease (Omim)	Inheritance	ACMG classification
Case 1	TRPV6	Intron 2	c.347–1G>A	Homozygous	Transient Neonatal Hyperparathyroidism	Autosomal recessive	Pathogenic
Case 2	TRPV6	Intron 2	c.347–1G>A	Homozygous	Transient Neonatal Hyperparathyroidism	Autosomal recessive	Pathogenic
Case 3	TRPV6	Intron 2	c.347–1G>A	Homozygous	Transient Neonatal Hyperparathyroidism	Autosomal recessive	Pathogenic
Case 4	TRPV6	Exon 8	c.1171C>T (p.Pro391Ser)	Homozygous	Transient Neonatal Hyperparathyroidism	Autosomal recessive	Unknown significance

[Table/Fig-4]: Genetic test reports.

with severe meconium aspiration syndrome. Due to severe respiratory distress, with SpO_2 at 80% in room air, the baby was intubated and placed on mechanical ventilation (synchronised intermittent mandatory ventilation mode). Antenatal ultrasonography showed polyhydramnios (AFI of 18), but no gastrointestinal anomalies and no maternal co-morbidities were noted.

On examination, the baby had a length of 46 cm, a head circumference of 33 cm, severe hypotonia, a narrow chest wall, and no dysmorphic features. The infantogram showed a bell-shaped thorax, multiple rib fractures, and generalised osteopenia [Table/Fig-5a-d]. Biochemical findings revealed normal serum calcium levels (8.5 mg/dL), normal phosphorus levels (4.8 mg/dL), elevated PTH (1966 pg/mL), and low vitamin D levels (6.5 ng/mL) [Table/Fig-2]. The mother's vitamin D levels were assessed on the 3rd postnatal day when she came from another hospital. As the mother had low vitamin D levels (10 ng/mL), the possibility of congenital rickets due to maternal vitamin D deficiency was considered. The baby was treated with calcitriol at a dosage of 20 ng/kg/day for three days, followed by vitamin D at 2000 IU/day for one week, and oral calcium at 500 mg/day. After one week, repeat serum calcium (9 mg/dL), serum phosphorus (4.4 mg/dL), and vitamin D levels (45 ng/mL) were normal, and PTH levels showed a decreasing trend (271 pg/mL).



[Table/Fig-5]: a-d) a) Infantogram at birth- bell shaped thorax, multiple rib fractures with callus; b) Osteopenia of long bones; c) X-ray lower limbs at 45 days age- improved bone density; d) Chest X-ray at 1 year 6 months- normal rib cage, normal bone density.

Congenital rickets classically presents with hypocalcaemic seizures. However, in this case, the normal calcium levels combined with elevated parathormone levels suggested secondary hyperparathyroidism (as hypercalcemia is typically seen in primary hyperparathyroidism). Therefore, genetic testing was conducted considering TNHP.

All biochemical parameters were normalising by four weeks. The baby was weaned from the ventilator to nasal CPAP on postnatal day 12, with respiratory support withdrawn by 28 days of age, and was discharged on postnatal day 31 with vitamin D at 400 IU/day. Exome analysis revealed a homozygous 3' splice site variation (c.347-1G>A) in intron 2 of the TRPV6 gene [Table/Fig-4].

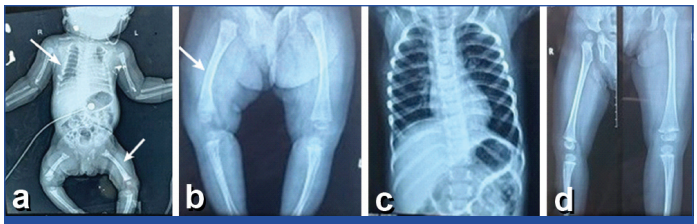
Case 4

A full-term, 39-week-old, first-born female child of a non consanguineous marriage to a 27-year-old primi mother was delivered by caesarean section (indication: thick meconium-stained amniotic fluid). The baby was appropriate for gestational age (birth weight: 2550 g) and was admitted to the neonatal intensive care unit with worsening respiratory distress soon after birth. The baby was depressed at birth, with a heart rate of less than 100 beats per minute, and was immediately ventilated, requiring inotropic support for compensated shock, likely due to perinatal asphyxia.

The baby was ventilated for two days, followed by nasal CPAP administration, and was gradually weaned off oxygen by two weeks. The mother had hypothyroidism (on thyroxine) and gestational diabetes (managed by diet). Antenatal ultrasonography showed oligohydramnios (AFI-3).

Upon examination, the baby had a length of 43 cm, a head circumference of 32 cm, a narrow chest wall, and severe hypotonia of all limbs.

The infantogram showed diffuse osteopenia with mild bowing of the femurs, thinned and short beaded ribs, suggestive of multiple rib fractures with callus [Table/Fig-6a-d]. Biochemical reports indicated normal serum calcium levels (8.2 mg/dL), normal phosphorus levels (4.5 mg/dL), elevated PTH (1347 pg/mL), and low vitamin D levels (11.05 ng/mL) [Table/Fig-2]. The mother's vitamin D levels were also low (10.5 ng/mL). Considering the diagnosis of congenital rickets, treatment was initiated with calcitriol at a dosage of 20 ng/kg/day for three days, followed by vitamin D at 2000 IU/day for one week, and intravenous calcium at 8 mL/kg/day for three days, followed by oral calcium at 500 mg/day. Vitamin D was administered as 2000 IU/day for one week, followed by 400 IU/day.



[Table/Fig-6]: (a-d) a) Infantogram at birth- narrow thoracic cage with multiple fracture ribs, osteopenia of long bones; b) X-ray lower limbs at 3 months age- improved bone density; c) At 1 year 9 months, Chest X-ray – normal; d) X-ray lower limbs - normal.

The baby was weaned off all respiratory support by two weeks of life and was discharged on postnatal day 20. A genetic study (next-generation sequencing) was conducted due to the suspicion of TNHP (as seen in a similar clinical presentation in a previous case), which revealed a homozygous missense variation (c.1171C>T: p.Pro391Ser) in exon 8 of the TRPV6 gene. This variation is classified as a variant of unknown significance according to ACMG guidelines [Table/Fig-4]. A parental exome study was advised for reclassification of the variant.

MANAGEMENT AND OUTCOME

All babies were treated with calcium and vitamin D [7]. Follow-up investigations showed normal biochemical parameters as early as two to four weeks (with varying durations for different cases) [Table/Fig-2]. There was complete resolution of clinical and radiological features by one year of age in case 1, and by one year and six months of age in two cases (case 3 and case 4). One baby (case 2) had mild bowing of the tibia persisting at one year and nine months. All babies are still under clinical follow-up.

DISCUSSION

The role of calcium and its constant supply to the foetus is very important for foetal bone formation and mineralisation, blood coagulation and neuromuscular activity. Foetal skeletal mineralisation depends on the active calcium transport through the placenta. After birth, calcium transport is predominantly maintained by the paracellular pathway in the intestines [8]. It has been identified that TRPV6, the sixth member of the TRPV subfamily, is a highly calcium-selective epithelial calcium channel protein that plays a crucial role in calcium transport [9,10]. The TRPV6 gene is located on chromosome 7q33-q34 and is expressed in the placenta and exocrine pancreas [11,12]. The functional TRPV6 channels comprise four identical subunits, each with six transmembrane segments (S1-S6), forming an inwardly rectifying calcium-selective ion channel. Suzuki Y et al., have reported that a mutation in the TRPV6 gene results in foetal hypocalcaemia and secondary hyperparathyroidism, leading to skeletal undermineralisation and increased bone resorption, which results in skeletal abnormalities [13]. Nett V et al., have described different mutations within the TRPV6 gene causing skeletal abnormalities in the foetus, when both alleles are affected in the foetal part of the placenta [14].

To date, only a few cases of TNHP caused by TRPV6 mutations have been reported in the literature [2,3,4,13,15,16] [Table/Fig-7].

It has been found that about 30 g of calcium accumulates in the foetus by term gestation. The maximum amount of calcium (about

Study	Place of origin	Number of cases	Clinical presentations		Age at complete resolution
			Prenatal	Postnatal	
Suzuki Y et al., 2018 [2]	Pakistan	6	Polyhydramnios, Bell shaped chest, short ribs	Respiratory distress	1.5 years
	Japan		Polyhydramnios, Short long bones	Respiratory distress	1.5 years
	Japan		Polyhydramnios, Short and bowed femurs	Respiratory distress	2 years
	Japan		Thoracic narrowing with rib deformities	Respiratory distress	2 years
	Japan		No abnormalities (USG at 20 weeks)	Respiratory distress	1 year
	Jamaica		Reportedly normal: not clear about USG	Respiratory distress	Still abnormal but substantial improvement
i) Burren CP et al., 2018 [3] ii) Mason AE et al., 2020 [4]	UK	1	Polyhydramnios, Small chest, Short long bones	Respiratory distress	Improved skeletal mineralisation till 4 months But expired due to volvulus, and multiorgan failure
Yamashita S et al., 2019 [15]	Japan	1	Not reported	Respiratory distress	1.5 years
Suzuki Y et al., 2020 [13]	Japan	2	Polyhydramnios, Bell shaped chest, short ribs	Respiratory distress	Still abnormal but substantial improvement
			No abnormalities detected	Respiratory distress	1.8 years
Almidani E et al., 2020 [16]	Riyadh, KSA	1	Polyhydramnios, Skeletal abnormalities (CVS – trio WES done)	Vigorous baby	1 month age- normal. Follow-up planned
Present study, 2025	India	4	Rhizomelic dwarfism, Suspected osteogenesis imperfecta	Uneventful postnatal period	1 year
			Polyhydramnios	Respiratory distress	1 year 9 months Mild bowing of femur
			Polyhydramnios	Respiratory distress	1 year 6 months
			Oligohydramnios	Respiratory distress	1 year 6 months

[Table/Fig-7]: Summary of case reports.

80%) is transported through the placenta during the third trimester, although materno-foetal calcium transfer begins at 12 weeks of gestation [17]. The maintenance of calcium balance in the foetus differs from that of a neonate in that the calcium levels in the foetus are higher than the levels in maternal circulation. This mechanism helps maintain foetal calcium homeostasis even if maternal calcium levels are low, thereby preventing neonatal hypocalcaemia and facilitating foetal bone mineralisation [1]. Abnormal findings in TNHP observed in antenatal ultrasonography, such as demineralised bones and multiple fractures, closely resemble those of osteogenesis imperfecta. The clinical presentation at birth includes respiratory distress and skeletal abnormalities, including generalised osteopenia, a narrow chest, short ribs with multiple fractures, and bowing of long bones.

Affected babies are usually born with respiratory distress soon after birth, requiring ventilatory support for a few weeks of life. Biochemical findings include low calcium and high PTH, suggestive of secondary hyperparathyroidism. Skeletal dysplasias with similar presentations in newborns include osteogenesis imperfecta, hypophosphatasia, and Neonatal Severe Hyperparathyroidism (NSHPT). Hypophosphatasia is caused by a loss-of-function mutation in the gene that encodes the Tissue Non-specific Isoenzyme of Alkaline Phosphatase (TNSALP), resulting in low serum alkaline phosphatase activity [18]. The causes of neonatal hyperparathyroidism can be primary, as in Calcium Sensing Receptor (CASR) mutations, which reduce the sensitivity of CASR to extracellular calcium, leading to increased secretion of PTH, decreased renal excretion of calcium, and hypercalcemia [19,20]. SLC12A1 mutations are associated with antenatal Bartter syndrome [21]. Pathogenic variants of the CASR gene may cause varying phenotypes, with biallelic variants resulting in NSHPT and monoallelic variants causing secondary hyperparathyroidism. Secondary neonatal hyperparathyroidism has been reported in mucolipidosis II, a lysosomal storage disorder with a clinical phenotype resembling Hurler syndrome, caused by GNPTAB mutations [22]. Maternal vitamin D deficiency can also result in similar skeletal changes, akin to congenital rickets [23,24]. Two of the cases had maternal vitamin D deficiency. Another very rare cause of NSHPT is maternal pseudohypoparathyroidism, potentially due to relative maternal hypocalcaemia during pregnancy [25]. It has been reported that vitamin D deficiency can coincide with TRPV6 variant cases, which were observed in all babies. TRPV6 expression is found to be strongly regulated by vitamin D [26,27].

Even though TNHP results from impaired calcium transport in-utero, adequate treatment with calcium will lead to the resolution of skeletal abnormalities. This is due to the postnatal change in calcium transport through the intestinal paracellular pathway, which facilitates the response to treatment with oral calcium, resulting in a good outcome. This observation is supported by studies of postmortem radiology and histology suggesting postnatal catch-up and recovery [4].

This case series highlights the importance of considering the diagnosis of TNHP in babies with skeletal changes resembling osteogenesis imperfecta. However, the biochemical abnormalities, non progressive course, and resolution after birth following treatment with calcium provide clues to consider the diagnosis of TNHP. Identification of this transient condition will help rule out lethal skeletal dysplasias and prompt the initiation of calcium therapy in newborns, thereby preventing disabilities. However, long-term follow-up with close monitoring of skeletal growth and development is recommended, along with subsequent assessment of bone mineral density, necessitating detailed studies in the future.

CONCLUSION(S)

Four cases of TNHP presented with similar skeletal changes characterised by poor bone mineralisation and multiple fractures of the ribs. Three babies experienced respiratory distress soon after birth, while one had an uneventful neonatal period. All subjects showed complete or partial resolution by approximately 18 to 24 months of age. Although a TRPV6 mutation causes insufficient calcium supply in-utero, clinical symptoms resolve during infancy when adequate calcium is provided. Thus, TNHP is unique due to its transient pathology in-utero and has a good prognosis, as it

responds well to calcium administration. In any case of suspicion, a skeletal survey and a biochemical and hormonal panel should be performed. Confirmatory genetic testing with exome sequencing will aid in diagnosis, allowing for appropriate treatment to be offered.

Acknowledgement

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